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Insulin-Like Growth Factor I and the Development of Colorectal Neoplasia in Acromegaly*

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ABSTRACT

Patients with acromegaly are at increased risk of colorectal neoplasia and, by analogy with high-risk nonacromegalic patients, may require regular colonoscopic screening. However, it is unknown whether the risk is equal in all patients or whether some should be regarded as carrying a particularly high risk. The aims of this study were: 1) to establish the natural history of colorectal neoplasia in acromegaly; 2) to establish which patients are at increased risk of developing neoplasia; and 3) to elucidate the influence of insulin-like growth factor I (IGF-I) in adenoma formation. A prospective colonoscopic evaluation of the development of new premalignant adenomas in the colon was performed in 66 patients with biochemically proven acromegaly who had previously undergone colonoscopic screening and removal of all visible polyps. Twenty-five patients (38%) had a total of 37 polyps detected at the second colonoscopy: nine (14%) had at least one adenoma, and 18 (27%) had one or more hyperplastic polyps (2 patients had both). The development of new adenomas, but not hyperplastic polyps, was associated both with elevated serum IGF-I ($P < 0.005$) and, to a lesser extent, with a previous adenoma at the original colonoscopy ($P < 0.07$). In summary, patients with acromegaly and in whom serum IGF-I remains elevated and/or who have had a previous adenoma should be regarded as having an especially high risk for the development of subsequent colorectal neoplasia. Serum IGF-I seems to be implicated in the development of colorectal neoplasia in acromegaly, although the exact mechanisms remain uncertain. (*J Clin Endocrinol Metab* **85:** 3218–3221, 2000)

ACROMEGALY IS associated with an increased prevalence of colorectal tubulovillous adenoma and carcinoma (1–17). In our series we observed 5% of patients to have a colorectal cancer and 25% to have one or more adenomas (18). In the nonacromegalic population, the vast majority of colorectal cancers arise from adenomas (hyperplastic polyps are nonneoplastic), a sequence thought to take approximately 10–15 yr (19), and which is associated with the progressive accumulation of mutations in oncogenes and tumor suppressor genes (20). Colorectal cancer is, thus, to some extent, a preventable disease; several studies have demonstrated that colonoscopic removal of visible polyps reduces the incidence of subsequent cancer (21–23). In the normal population, it has been suggested that a single screening at 55 yr may be sufficient, but known high-risk groups such as patients with ulcerative colitis or a family history of hereditary nonpolyposis colonic carcinoma are offered more regular screening at 1–5 yearly intervals. It is likely that this principle should also apply to patients with a history of acromegaly, but it is currently uncertain how often screening should be offered. This is particularly important because colonoscopy in acromegalics is associated with practical difficulties: 1) they have an increased large bowel transit time and require prolonged and rigorous bowel preparation for optimal visualization, which usually necessitates hospital admission (24); and 2) the increased length, particularly of the sigmoid, and diameter of the colon increases the difficulty and duration of the procedure (25).

In addition, it is unknown whether the natural history of colorectal neoplasia in acromegaly is the same as in the nonacromegalic population and how it is influenced by disease activity and circulating insulin-like growth factor I (IGF-I). The previous epidemiological studies of the prevalence of colorectal neoplasia in acromegaly have been unable to clarify this issue because it is uncertain how long any adenomas/carcinomas had been present at the time of surveillance. Establishing the true incidence of these lesions in acromegaly requires careful prospective surveillance after a previous colonoscopy has removed all visible polyps.

The aims of the current study were, therefore: 1) to establish the natural history of colorectal neoplasia in acromegaly; 2) to establish which patients are at increased risk of developing colorectal neoplasia; and 3) to elucidate the influence of IGF-I in adenoma formation.

Patients and Methods

Clinical features of the patients

Sixty-six patients with acromegaly underwent a repeat colonoscopic examination at varying intervals (mean, 32.7 months; range, 3–76) after their original screening colonoscopy, at which all visible polyps were removed. The patients were not specifically selected and represent consecutive patients; no patient refused repeat colonoscopy, and none had any risk factors for colorectal cancer. The interval between the first and

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second colonoscopy was selected according to the suggestions of the endoscopist at the original colonoscopy. All patients gave informed consent. At the time of the repeat examination, one patient had coexisting carcinoma of the pancreas with extensive hepatic metastases, but no other patient had symptoms relating to gastrointestinal disease. The mean age at this second colonoscopy was 63.3 yr (range, 42–85).

Bowel preparation

All patients received 2 L of the osmotic purgative Klean-Prep (Norgine Ltd., Harefield, UK) at 6, 4, and 2 h (total 6 L or more) before the procedure with a liquid-only diet for 24 h beforehand. Oral iron was stopped at least 1 week before the start of the preparation. Colonoscopic examination was performed using an Olympus (Southend-on-Sea, UK) long colonoscope (CF IOTL or CF 230L) by the same operator (P.D.F.) who had performed the original examination, except in one patient who had undergone initial colonoscopy at a different institution 18 months previously. Any lesion visualized was recorded and removed by snare diathermy or hot biopsy and placed in formalin for subsequent histological assessment by a single pathologist (D.G.L.).

GH and IGF-I measurements

Serum IGF-I was assayed using an in-house RIA after formic acid-acetone extraction, as described previously (26). Age-related reference ranges were established in the same laboratory using serum derived from 150 healthy blood donors. The inter- and intra-assay coefficients of variation were less than 10%. Serum GH was assayed by immunoradiometric assay (North East Thames Regional Immunoassay Laboratory, St. Bartholomew's Hospital; inter- and intra-assay CV, <8%).

Statistics

Normality of data was assessed by the Kolmogorov-Smirnov test using the SPSS 8.0 software package (SPSS Inc., Chicago, IL). The Student's *t* test was used for between group comparison of normally distributed data, whereas analysis of nonparametric data was performed using the Mann-Whitney *U* test and Fisher's exact test. Significance was taken as *P* less than 0.05.

Results

At the second colonoscopy, the colon was visualized to the caecum in all 66 patients. Twenty-five patients (38%) had a total of 37 polyps detected: nine (14%) had at least one adenoma and 18 (27%) had one or more hyperplastic polyps. Two patients had both an adenoma and a hyperplastic polyp. A carcinoma was discovered in the transverse colon of the patient who had undergone the first screening colonoscopy at a different institution. This examination had been reported as normal as far as the ascending colon. The anatomical location of the polyps within the colon is shown in Table 1. The size of the 14 adenomas was less than 1 cm in all but one. Nine were mildly dysplastic, and five exhibited moderate dysplasia. The minimum age of the patients with a new adenoma was 55 yr, and their clinical characteristics compared with those patients with either a hyperplastic polyp or normal colon are detailed in Table 2. There was no relation between duration of disease and the development of new adenoma.

TABLE 1. The anatomical location of new polyps and adenomas detected at repeat colonoscopic examination in 66 patients with acromegaly

Location of polyp	All polyps	Adenoma
Caecum	5	3
Ascending colon	3	1
Transverse colon	7	5
Descending/sigmoid colon	10	4
Rectum	12	1
Total	37	14

Relation between polyps and serum IGF-I

For this analysis, the patient with metastatic pancreatic cancer was not included. The eight remaining patients with a new adenoma had a significantly elevated serum IGF-I level compared with those patients with either a hyperplastic polyp or normal colon (mean ± SEM, 390 ± 57 *vs.* 268 ± 36 *vs.* 244 ± 18 ng/mL, respectively; $P < 0.005$; Table 2 and Fig 1). Among the eight patients with a new adenoma, the mean percentage increase in the serum IGF-I level above the maximum of the age-corrected normal range was 156%. Among all patients, 26 patients had an elevated IGF-I at the second colonoscopy. Of these, seven patients had a new adenoma compared with one patient with an IGF-I within the age-corrected normal range ($P < 0.004$; relative risk, 10.8). Six of the 26 patients with an elevated serum IGF-I had a hyperplastic polyp compared with 12 of the 40 patients with a normal IGF-I ($P > 0.05$).

Relationship to previous colonic neoplasia

At the original screening, 32 patients had had at least one neoplasm removed [antecedent neoplasms (AN); twenty nine had an adenoma and five had a carcinoma]. The remaining 34 patients had had no neoplasm detected [no antecedent neoplasm (NAN)]. There was no significant difference between the two groups at the second colonoscopy in either the age (mean ± SEM) of patients (AN *vs.* NAN; 64.3 ± 1.7 *vs.* 62.3 ± 1.8 yr) or serum IGF-I (AN *vs.* NAN; 279 ± 26 *vs.* 229 ± 19.9 ng/mL), but the interval between the first and

TABLE 2. The clinical characteristics of 66 patients with acromegaly with and without a new tubulovillous adenoma detected at the second colonoscopy

	Patients with new adenoma (n = 9) mean (SEM)	Patients without new adenoma (n = 57) mean (SEM)	*P*
Age (yr)	65.8 (2.0)	62.9 (1.4)	n.s.
Interval since first colonoscopy (months)	30.1 (4.5)	33.1 (2.3)	n.s.
Mean duration of acromegaly since onset of symptoms (yr)	26.1 (7.9)	20.5 (8.2)	n.s.
Number receiving octreotide	4 (44%)	14 (24%)	n.s.
GH at first colonoscopy (ng/mL)	28 (11.4)	27.8 (6.4)	n.s.
GH at second colonoscopy (ng/mL)	28.2 (13.4)	13.4 (2.0)	<0.05
IGF-I at first colonoscopy (ng/mL)	458 (118)	322 (29)	n.s.
IGF-I at second colonoscopy (ng/mL)	390 (57)	231 (15)	<0.005

n.s., $P > 0.05$.

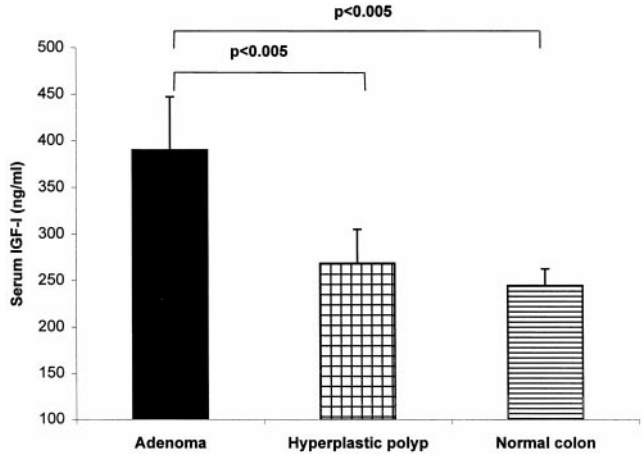

FIG. 1. The mean (±SEM) serum IGF-I at the second colonoscopy in 66 patients with acromegaly with colorectal adenomas, hyperplastic polyps, or normal colon.

second colonoscopy was significantly shorter for patients with AN compared to NAN (26.2 ± 2.6 *vs.* 39.2 ± 3.0 months, $P < 0.002$).

Seven of the patients with new adenomas were in the AN group compared with two patients with a new adenoma in the NAN group ($P < 0.07$), one of whom was the patient with the newly discovered carcinoma. One of the seven patients had had a previous carcinoma.

Ten patients subsequently underwent a third colonoscopy, at a mean interval of 19.8 months (range, 6–31) after the second colonoscopy. At this third screening, two patients (aged 72 and 73 yr) had a new adenoma, with one patient having three lesions. Both patients had also had adenomas at the second colonoscopy, and they had the highest serum IGF-I levels at both second and third colonoscopies (percentage above the upper limit of age-corrected normal range, 164% and 240%).

Discussion

Recent prospective epidemiological evidence has implicated serum IGF-I in colorectal cancer. Nonacromegalic subjects with serum IGF-I in the upper quintile of the normal range have a 2.5-fold increased risk of developing colorectal cancer compared with subjects with IGF-I in the lowest quintile (27). Our findings suggest that circulating IGF-I is also implicated in the increased risk of colorectal neoplasia among patients with acromegaly. Patients with an adenoma visualized at their repeat colonoscopic screening had significantly higher serum IGF-I levels compared with acromegalic patients without a new adenoma. The relative risk of developing a new adenoma was 10.3 if the serum IGF-I was above the upper limit of the age-corrected normal range. Previous epidemiological studies investigating the prevalence of colorectal neoplasia failed to demonstrate any difference in IGF-I levels between patients with and without neoplasia (1, 2, 5, 8–10, 12–15). However, all of these, including the large study from this institution (18), were in effect retrospective studies; it is unknown how long the adenomas had been present before being detected. Determination of the true incidence and the role of IGF-I can only be established by performing repeat colonoscopy at intervals after the original screening examination when all visible lesions were removed. Although it is possible that some small polyps might have been missed on the first colonoscopy and subsequently detected at the second, such a bias would have occurred equally among all the patients and would not have been restricted to those with elevated IGF-I. Moreover, in every patient but one, the examination was performed on both occasions by the same operator who was able to visualize the entire colon in all patients.

The demonstrated association between elevated circulating IGF-I and adenoma formation suggests that IGF-I acts early in the epithelium-adenoma-carcinoma sequence, rather than (or in addition to) promoting the progression from adenoma to carcinoma. This early role is supported by immunohistochemical studies on mucosal cell proliferation of colorectal crypts. Patients with acromegaly have significantly increased proliferation of the colonic crypt epithelium, as evidenced both by incorporation of 5-bromo-2′-deoxyuridine and by the number of cells undergoing mitosis in microdissected crypts (28, 29). In both of these studies the increased proliferation correlated with serum IGF-I. Studies using colorectal cancer cell lines *in vitro* also support a role for systemic IGF-I in stimulating colonic epithelial proliferation (30, 31).

In addition to elevated serum IGF-I, another indicator of increased risk of colonic neoplasia among patients with acromegaly seems to be the presence of a previous adenoma. Seven of the nine patients with a new adenoma had had one or more removed at the original colonoscopic screening. Of interest is the patient who underwent the screening colonoscopy at a different institution; at that time the hepatic flexure was reported to be normal, but the second examination 18 months later revealed a carcinoma in the transverse colon and four adenomas. Although these lesions have been classified as being new, it is probable that instead they were missed at the original screening, again emphasizing the need for visualization to the caecum by an experienced operator. Exclusion of this patient's findings from the analysis strengthens the significance for a previous adenoma being a risk factor for subsequent neoplasia (relative risk, 6.8; $P < 0.03$). Whether this increased risk associated with previous adenoma reflects a generalized hyperproliferative colonic epithelium among patients with an original adenoma, or an additional pathogenetic factor other than IGF-I, remains to be determined. The latter is suggested by the absence of any relation between IGF-I levels and the development of hyperplastic polyps that are not thought to be premalignant.

The findings from this study allow some initial suggestions about colonoscopic screening in patients with acromegaly. Those with either active disease, as evidenced by an elevated IGF-I, and/or an adenoma seem to be at greatest risk of developing further neoplastic polyps, which if left might lead to eventual carcinoma. An additional factor is the age of the patients. In our original survey of the prevalence of colonic neoplasia, age was a significant factor, whereas in this prospective survey the youngest patient to develop a new adenoma was 55-yr-old. Because the mean interval between the first and second colonoscopy in patients with adenoma was 2.5 yr (shortest interval 11 months), we suggest

three yearly total colonoscopy is reasonable for patients over the age of 55 yr with either an elevated serum IGF-I or a previous adenoma. For patients who are either 'cured' of their disease or who have a normal screening colonoscopy, five yearly screening might be appropriate. Needless to say, these initial recommendations may need to be modified with further long-term follow-up studies of larger numbers of patients.

In conclusion, this study not only demonstrates the need for long-term surveillance colonoscopic screening of patients with acromegaly, but also suggests that the development of colorectal neoplasia in these patients is related to disease activity and previous neoplasia. In common with the other morbidity associated with this disease, this neoplasia might be minimized by aggressive reduction of circulating GH and IGF-I.

References

1. **Klein I, Parveen G, Gavaler JS, Vanthiel DH.** 1982 Colonic polyps in patients with acromegaly. Ann Intern Med. 97:27–30.
2. **Klein I.** 1984 Acromegaly and cancer. Ann Intern Med. 101:706–707.
3. **Ritter MM, Richter WO, Schwandt P.** 1987 Acromegaly and colon cancer. Ann Intern Med. 106:636–637.
4. **Ziel FH, Peters AL.** 1988 Acromegaly and gastrointestinal adenocarcinomas. Ann Intern Med. 109:514–515.
5. **Brunner JE, Johnson CC, Zafar S, et al.** 1990 Colon cancer and polyps in acromegaly: increased risk associated with family history of colon cancer. Clin Endocrinol. 32:65–71.
6. **Barzilay J, Heatley GJ, Cushing GW.** 1991 Benign and malignant tumors in patients with acromegaly. Arch Intern Med. 151:1629–1632.
7. **Ezzat S, Strom C, Melmed S.** 1991 Colon polyps in acromegaly. Ann Intern Med. 114:754–755.
8. **Ezzat S, Melmed S.** 1991 Clinical review 18: are patients with acromegaly at increased risk for neoplasia? J Clin Endocrinol Metab. 72:245–249.
9. **Pines A, Rozen P, Ron E, Gilat T.** 1985 Gastrointestinal tumors in acromegalic patients. Am J Gastroenterol. 80:266–269.
10. **Ron E, Gridley G, Hrubec Z, Page W, Arora S, Fraumeni Jr JF.** 1991 Acromegaly and gastrointestinal. Cancer. 68:1673–1677.
11. **Smith MB.** 1991 Colonic polyps in acromegaly. Ann Intern Med. 115:232–233.
12. **Vasen HF, van Erpecum KJ, Roelfsema F, et al.** 1994 Increased prevalence of colonic adenomas in patients with acromegaly. Eur J Endocrinol. 131:235–237.
13. **Terzolo M, Tappero G, Borretta G, et al.** 1994 High prevalence of colonic polyps in patients with acromegaly. Influence of sex and age. Arch Intern Med. 154:1272–1276.
14. **Ortego J, Vega B, Sampedro J, Escalada J, Boixeda D, Varela C.** 1994 Neoplastic colonic polyps in acromegaly. Horm Metab Res. 26:609–610.
15. **Delhougne B, Deneux C, Abs R, et al.** 1995 The prevalence of colonic polyps in acromegaly: a colonoscopic and pathological study in 103 patients. J Clin Endocrinol Metab. 80:3223–3226.
16. **Colao A, Balzano A, Ferone D, et al.** 1997 Increased prevalence of colonic polyps and altered lymphocyte subset pattern in the colonic lamina propria in acromegaly. Clin Endocrinol. 47:23–28.
17. **Archambeaud-Mouveroux F, Geffray I, Teissier MP, Galinat S, Sautereau D, Pillegand B.** 1998 Prevalence of colorectal carcinoma and polyps in acromegaly. Presented at the 80th Annual Meeting of The Endocrine Society, New Orleans, LA, 1998; P2–504.
18. **Jenkins PJ, Fairclough PD, Richards T, et al.** 1997 Acromegaly, colonic polyps and carcinoma. Clin Endocrinol. 47:17–22.
19. **Muto T, Bussey HJ, Morson BC.** 1975 The evolution of cancer of the colon and rectum. Cancer. 36:2251–2270.
20. **Fearon ER, Vogelstein B.** 1990 A genetic model for colorectal tumorigenesis. Cell. 61:759–767.
21. **Atkin WS, Morson BC, Cuzick J.** 1992 Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. N Engl J Med. 326:658–662.
22. **Atkin WS, Cuzick J, Northover JM, Whynes DK.** 1993 Prevention of colorectal cancer by once-only sigmoidoscopy. Lancet. 341:736–740.
23. **Winawer SJ, Zauber AG, Ho MN, et al.** 1993 Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med. 329:1977–1981.
24. **Veysey MJ, Thomas LA, Mallet A, et al.** 1999 Prolonged large bowel transit increases serum deoxycholic acid: a risk factor for octreotide induced gallstones. Gut. 44:675–681.
25. **Jenkins PJ, Mills TD, Veysey MJ, Reynolds CR, Dowling RH, Besser GM.** 1997 Acromegaly is associated with colonomegaly which correlates with tissue exposure to growth hormone and may be implicated in their increased risk of colorectal neoplasia. Journal of Endocrinology 155:OC22.(Abstract)
26. **Morrell DJ, Dadi H, More J, et al.** 1989 A monoclonal antibody to human insulin-like growth factor-I: characterization, use in radioimmunoassay and effect on the biological activities of the growth factor. J Mol Endocrinol. 2:201–206.
27. **Ma J, Pollak M, Giovannucci E, et al.** 1999 Prospective study of colorectal cancer risk in men and plasma levels of insulin like growth factor (IGF)-1 and IGF-binding protein-3. J Natl Cancer Inst. 91:620–625.
28. **Cats A, Dullaart RP, Kleibeuker JH, et al.** 1996 Increased epithelial cell proliferation in the colon of patients with acromegaly. Cancer Res. 56:523–526.
29. **Stellini M, Jenkins PJ, Fairclough P, et al.** The pathogenesis of colorectal neoplasia in acromegaly (Abstract PO955). United European Gastroenterology Week, Rome, Italy, 1999.
30. **Durrant LG, Watson SA, Hall A, Morris DL.** 1991 Co-stimulation of gastrointestinal tumour cell growth by gastrin, transforming growth factor α and insulin like growth factor-I. Br J Cancer. 63:67–70.
31. **Lahm H, Suardet L, Laurent PL, et al.** 1992 Growth regulation and co-stimulation of human colorectal cancer cell lines by insulin-like growth factor I, II and transforming growth factor α. Br J Cancer. 65:341–346.